

## Emerging role of Fatty acid synthase in tumor initiation: implications for cancer prevention

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### ABSTRACT

Targeting metabolic reprogramming has emerged as a promising strategy for therapeutic intervention in cancer. We identify that fatty acid synthase (FASN) is essential for cancer initiation playing a critical role in acquiring three-dimensional (3D) growth properties during transformation. *In vivo* inhibition of FASN before oncogenic activation prevents tumor development and invasive growth suggesting that FASN could be a potential target for cancer prevention.

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Fatty acid synthase (FASN) is a multienzyme protein that catalyzes the synthesis of fatty acids from acetyl-CoA and malonyl-CoA in a nicotinamide adenine dinucleotide phosphate-reduced (NADPH)-dependent reaction in mammalian cells. Most normal adult tissues have low levels of FASN expression and activity; therefore, they preferentially satisfy their fatty acid needs by uptaking circulating lipids from the diet.<sup>1</sup> Many human carcinomas exhibit elevated levels of FASN and present a correlation between higher levels of FASN with later stages of the disease and poor prognosis strengthening the hypothesis of a potential oncogenic role of FASN.<sup>2,3</sup> Considering that in adult mice, lethality is only observed in the case of conditional deletion of FASN in the gastrointestinal tract,<sup>4</sup> FASN inhibition is presented as a new therapeutic opportunity for cancer treatment. Early generation of FASN inhibitors have been tested preclinically, unfortunately, modest antitumor effects, limited pharmacologic properties, and off-target effects impair its transition to human clinical trials.<sup>5</sup> In recent years, modern, advanced and potent FASN inhibitors are being studied preclinically but only TVB-2640 has entered clinical evaluation in oncology. Although a favorable tolerability profile was found in patients and prolonged stable disease has been seen with monotherapy, preliminary results do not indicate that targeting FASN may eradicate established tumors.<sup>6</sup>

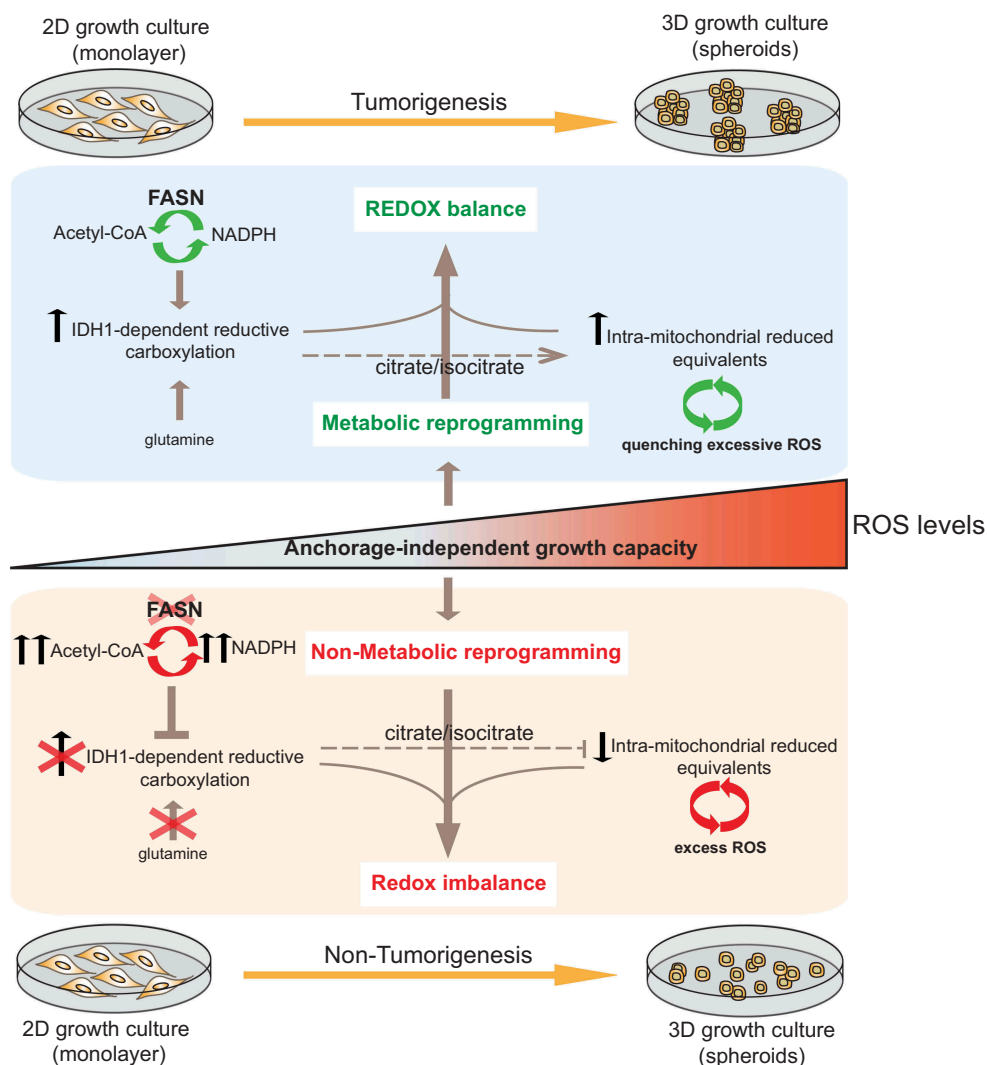
Despite FASN has been extensively studied in cancer, its specific mechanistic relationship with carcinogenesis, and its definitive therapeutic role in cancer, have not been completely established. However, some of these studies may be limited by certain conditions, cells are often cultured as monolayer which do not faithfully reflect the physiologic situation *in vivo*, where cancer cells need to detach, migrate, and invade. Three-dimensional (3D) cell culture models, such as spheroids, resemble more closely the *in vivo* situation, where the ability to grow in 3D in the absence of intercellular matrix

attachment is a necessary hallmark that transforming cells must acquire to develop clinical tumors.

Our recent findings highlight the involvement of FASN in the metabolic reprogramming events that occur during tumor initiation facilitating the transition from Two-dimensional (2D) to 3D growth and demonstrated that overexpression of FASN appears to play a key element in the pathway to establishing tumorigenicity in previously normal cells.

In 2016, Jiang and colleagues showed that anchorage-independent growth, a property of most malignant cells, promotes mitochondrial oxidative stress that must be counterbalanced by isocitrate dehydrogenase 1 (IDH1)-driven changes in reductive carboxylation and citrate metabolism.<sup>7</sup> Using several *in vitro* and *in vivo* models we demonstrated that FASN upregulation is critical for eliciting the switch from 2D to 3D growth sustaining the IDH1-dependent reductive carboxylation of glutamine. FASN loss produces an acetyl-CoA accumulation that could block the activity of adenosine triphosphate (ATP) citrate lyase, impeding the buildup of cytoplasmic citrate/isocitrate that would stall the IDH-dependent reductive carboxylation. In this situation, there would be insufficient intra-mitochondrial reduced equivalents, which would be consumed by the excess of unquenched reactive oxygen species (ROS) produced during the 2D to 3D transition.<sup>8</sup> Thus, an excess of ROS could account for the inability to transform in the absence of FASN and suggest a possible metabolic intervention to suppress anchorage independence (Figure 1). The *in vivo* implications of these effects were studied in different mouse models. Since in the absence of FASN, the breast epithelium cannot undergo a transformation, the benefit of targeting FASN before rather than after transformation deserves to be studied in depth.

For the first time, FASN upregulation has been linked to a critical role in acquiring 3D growth properties during transformation, unrelated to its biosynthetic product. Considering the lack of essentiality in most adult tissues and due to the



**Figure 1.** FASN is essential in the 2D-to-3D growth transition of transforming cells. During the initial steps of the malignant transformation process, FASN consumes adenine dinucleotide phosphate-reduced (NADPH) and acetyl-CoA, which unlocks isocitrate dehydrogenase 1 (IDH1)-dependent reductive carboxylation, producing the reductive power necessary to quench reactive oxygen species originated during the switch from 2D to 3D growth, a hallmark of cancer. However, in the absence of FASN, the production of reduced equivalents from IDH1-dependent reductive carboxylation to quench the excessive reactive oxygen species (ROS) observed in the 2D-3D transition is impaired (cell redox imbalance), which accounts for the inability to transform.

specificity of the IDH1-dependent reductive carboxylation process in cancer cells, FASN has emerged as a potential target for cancer prevention studies.

Nowadays, preventive therapy may be applied to healthy people at high risk for the development of breast cancer based on the Gail model, to patients with premalignant conditions to reduce the probability of development of invasive cancer, and to patients already treated for cancer to prevent a recurrence. Two selective estrogen-receptor modulators, tamoxifen and raloxifene, are so far the main medical options approved by the Food and Drug Administration (FDA) for breast cancer prevention. Although the benefit of these preventive therapies has been extensively validated in several clinical trials,<sup>9</sup> the acceptance of tamoxifen or raloxifene for reducing the risk of breast cancer has been poor, in part because they are both associated with rare but serious toxic effects.<sup>10</sup>

To keep the devastating impact of breast cancer to a minimum, much greater efforts are needed in the area of

cancer prevention. Given the importance of FASN in the metabolic reprogramming events that occur during transformation, novel FASN inhibitors that would selectively target FASN and could be administered long term to healthy people at high risk for cancer development represent a great opportunity for cancer prevention. In addition, future studies with clinical-grade compounds in high-risk patient subpopulations could address the therapeutic utility of this strategy.

#### Disclosure of Potential Conflicts of interest

No potential conflicts of interest were disclosed.

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